Randomized Sampling Can Measure the Size of Phenotypic Solution Spaces and How They Are Reduced by Successive Imposition of Constraints

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Constraint-based models in biology have been formulated and successfully used to analyze genome-scale networks. This approach relies on the statement of governing constraints and optimization procedures to determine particular solutions. To obtain a broader view of this analytical approach, we use uniform random sampling procedures of points in defined concentration solutions spaces to assess the reduction in the size of the solution space with the imposition of additional constraints. The additional constraints imposed in this study are thermodynamic constraints and concentration measurements. In addition, the large number of allowable solutions obtained enables us to calculate the expected values of individual variables and their variance within the solution space. These properties for individual variables can be recomputed as the solution space is shrunk with the imposition of additional constraints. This procedure is applied to a simple example system as well as real metabolic networks. The key results obtained are: (1) Monte Carlo sampling can measure the size, expected value, and variance of metabolite concentrations, (2) thermodynamic constraints are generally less constraining than concentration constraints, (3) non-linear thermodynamic constraints may segment a space into linear or non-linear subspaces, (4) non-linear constraints may reduce the solution space into a non-convex space, (5) spontaneous reactions, i.e. reactions with large ΔG_o, are less constraining than reactions with small K_{eq}, (6) the size reduction by the concentration constraints depend on the experimental error associated with the numerical value and where the number falls within the concentration space, and (7) the redundancy of constraints can be qualified over given metabolite regions. This study has initiated the broader characterization of the constrained solution spaces that result from biochemical network reconstructions to measure their size and the expected value of individual variables in the solution.

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